REGARDING MANAGING BIPOLAR DEPRESSION

DEAR EDITOR:

I would like to offer some comments on the article by Pary, et al., entitled "Managing Bipolar Depression." which was published in the February issue of *Psychiatry 2006* [*Psychiatry 2006* 2006;3(2):30–41]. First, Dr. Pary and colleagues should be commended for emphasizing that the treatment of bipolar disorder should focus on the disease entity itself and not merely on the acute episodes of mania or depression. This is particularly true when deciding whether and how long to utilize an antidepressant. Indeed, there are serious questions regarding the long-term utility of antidepressants in bipolar illness, aside from their potential for inducing a "switch" into mania.

I realize that a review cannot delve into the methodology of each study cited, and that several new studies have come out since the authors' article was prepared. However, it is important to note serious limitations in some studies cited in apparent support of antidepressant use in bipolar disorder. For example, the Altshuler, et al., study[1] was observational, not randomized, and did not include rapid-cycling patients. It cannot be taken as firm evidence that all bipolar depressed patients should be maintained on antidepressants for the long-term, though a subgroup may require such treatment. The Gijsman, et al., meta-analysis,[2] which appeared to show little risk of antidepressant-induced mania, did not review studies longer than 10 weeks in duration—a very short interval in the life of bipolar patients.

Furthermore, the Stanley Foundation Network[3] has just analyzed the results of a randomized acute and maintenance treatment study of bipolar depression and found that antidepressant-related switches into hypomania and mania occurred in 11.4 and 7.9 percent, respectively, of the acute treatment trials; and in 21.8 and 14.9 percent, respectively, of the continuation trials. Longer-term switch rates continued to accumulate with the three agents studied (venlafaxine, bupropion, and sertraline). These are far from comforting numbers. Similarly, a preliminary analysis of the randomized STEP-BD study[4] concluded that antidepressants have no added benefit in the long-term (one-year) treatment of bipolar patients who initially responded to antidepressants plus mood stabilizers.

Thus, while there may be no consensus regarding the treatment of acute bipolar depression, there is a growing consensus from randomized studies that long-term antidepressant use provides little benefit, and poses some risk, in the majority of bipolar patients.

The final comment I wish to make is that I believe there is an error in Table 7. It indicates that Paxil is "FDA approved for bipolar disorder." To my knowledge, and based on a check of the recent Paxil prescribing information, I do not believe that is the case.

REFERENCES

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2. Gijsman HJ, Geddes JR, Rendell JM, et al. Antidepressants for bipolar depression: A systematic review of randomized controlled trials. *Am J Psychiatry* 2004;161:1537–47.
3. Leverich GS, Altshuler LL, Fry MA, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. *Am J Psychiatry* 2006;163:232–9.
4. Ghaemi SN, El-Mallakh RS, Baldassano CF, et al. A randomized clinical trial of efficacy and safety of long-term antidepressant use in bipolar disorder (abstract). *Bipolar Disorders* 2005;7(Suppl 2):59.

With regards,
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AUTHOR RESPONSE

Dr. Pies is correct in mentioning that review articles usually do not delve into the methodology of the cited studies. We did not focus extensively on this aspect of the referenced articles. We accept Dr. Pies's comments on the limitations of the Altshuler[1] study and of the Gijsman[2] meta-analysis without rebuttal.

In so far as the Stanley Foundation Network article, they do state that "the current findings are highly suggestive *but not definitive*"[3] (italics ours). They mention that, "antidepressant augmentation in general is not likely to yield a high rate of sustained response without a switch throughout both the acute and continuation treatment phases."[3] Another report concluded that depressed patients with bipolar II disorder are less vulnerable than those with bipolar I disorder to switch into hypomania/mania when treated with an antidepressant adjunctive to a mood stabilizer.[4]

Putting all of this information together and treating the bipolar patient with depression is still one of the most challenging

aspects of clinical psychiatry. Our first choice in this regard is a combination of lithium with lamotrigine.

But what of depressed patients who are refractory to this combination or intolerant of side effects? It is well known that bipolar patients spend two thirds of their time depressed. Do antidepressants add to this risk? Increased antidepressant exposure was not associated with new-onset suicidality in a prospective study of participants in the systematic treatment enhancement program for bipolar disorder.[5] It is important to treat the depression and prevent possible depression-related suicide. Then the clinician can taper the antidepressant as warranted.

The use of an antidepressant in the long-term treatment of bipolar depression remains highly controversial. A recent study of long-term antidepressant use in bipolar patients found either "non-inferiority or slight superiority" when an antidepressant was discontinued as compared to being continued.[6] Is there a serious danger associated with discontinuing an antidepressant, however? In a 2003 study, it was reported that the risk for depressive relapse in bipolar patients is significantly associated with discontinuing an antidepressant soon after remission.[1] Thus, continued use of antidepressant drugs is both supported and refuted in the literature

It is our contention that the treatment of bipolar depression begins with an individualized approach. The clinician treating the patient must take all relevant information at his disposal and decide on how long to treat his depressed patient. Some depressed bipolar patients may require and benefit from an antidepressant/lithium combination despite the risk for switching into mania or hypomania. For example, we would offer a seriously depressed bipolar II patient with recent suicidal behavior as a candidate for an adjunctive antidepressant/lithium combination. If this hypothetical patient lacked a rapid cycling history, refused electroconvulsive treatment, and failed a trial of lamotrigine in the past, he would be an even better candidate for adjunctive antidepressant/lithium treatment in our opinion. It is the art of clinical psychiatry to know when to prescribe and not to prescribe such a regimen.

Finally, we wish to thank Dr. Pies for pointing out our error in stating that paroxetine was FDA approved for bipolar disorder. It is apparent that we inadvertently left out the word "Not" in front of "FDA approved". Our remark should have been that *paroxetine is not FDA approved for bipolar disorder*.

REFERENCES

1 Altshuler L, Suppes T, Black D, et al. Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year followup. *Am J Psychiatry* 2003;160:1252–62

2 Gijsman HJ, Geddes JR, Rendell JM, et al. Antidepressants for bipolar depression: A systematic review of randomized controlled trials. *Am J Psychiatry* 2004;161:1537–47.

3 Leverich GS, Althsuler LL, Fry MA, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline and bupropion as adjuncts to mood stabilizers. *Am J Psychiatry* 2006;163:232–39.

4 Altshuler LL, Suppes T, Black DO. Lower switch rates in depressed patients with bipolar II than bipolar I disorder treated adjunctively with second-generation antidepressants. *Am J Psychiatry* 2006;163(2):313–5.

5 Bauer MS, Wisniewski SR, Marangell LB, et al. Are Antidepressants associated with new-onset suicidality in bipolar disorder? A prospective study of participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *J Clin Psychiatry* 2006;67(1):48–55.

6 Ghaemi SN, El-Mallakh RS, Baldassano CF, et al. A randomized clinical trial of efficacy and safety of long-term antidepressant use in bipolar disorder. *Bipolar Disorders* 2005;7 (suppl 2):27–117

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